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Improved Suppression of Recurrent Atrial Fibrillation With Dual-Site Right Atrial Pacing and Antiarrhythmic Drug Therapy

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OBJECTIVES We compared the safety, tolerance and effectiveness of overdrive high right atrial (RA), dual-site RA and support (DDI or VDI) pacing (SP) in patients with symptomatic atrial fibrillation (AF) and bradycardias.

BACKGROUND Optimal pacing methods for AF prevention remain unclear.

METHODS Patients (n = 118) were randomized to each of three pacing modes in a crossover trial.

RESULTS Mode adherence was superior for dual-site RA (5.8 months) compared with SP (3.3 months; $p < 0.001$) and high RA pacing (4.7 months; $p = 0.006$). Adverse event-free survival improved with dual-site RA ($p = 0.007$ vs. SP) and was comparable to high RA ($p = 0.75$). AF-free survival trended to improve with dual-site RA (hazard ratio [HR] 0.715, $p = 0.07$ vs. SP) but not high RA (HR = 0.71, $p = 0.19$) or when dual-site RA was compared with high RA (HR = 0.835, $p = 0.175$). Time-to-recurrence was longer in dual-site RA (1.77 months) compared with high RA (0.62 months, $p < 0.09$) or SP (0.44 months, $p < 0.05$). In antiarrhythmic drug-treated patients, dual-site RA reduced recurrence risk compared with SP (HR = 0.638, $p = 0.011$) and high RA (HR = 0.669, $p = 0.06$). In patients with ≤1 AF event/week, dual-site RA improved AF suppression (HR = 0.464, $p = 0.004$ vs. SP; HR = 0.623, $p = 0.006$ vs. high RA). Dual-site RA improved AF-free and mode survival ($p < 0.03$ vs. high RA, $p < 0.001$ vs. SP) and reduced asymptomatic AF ($p < 0.01$ vs. high RA).

CONCLUSIONS Dual-site RA is safe and better tolerated than high RA and SP. In patients on antiarrhythmics, dual-site RA prolonged and high RA trended to prolong time-to-recurrent AF compared with SP. Dual-site RA provides superior symptomatic and asymptomatic AF prevention compared with high RA in patients with symptomatic AF frequency of ≤1/week. (J Am Coll Cardiol 2002;40:1140–50) © 2002 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is a highly prevalent arrhythmia and a recognized risk factor for stroke and excess mortality (1). Recurrence of AF is common during antiarrhythmic drug treatment, often progressing to permanent AF (2–4). Atrial pacing has reduced the incidence of permanent AF in patients with bradycardias (5,6). Recently dual-site right atrial (RA) and biatrial pacing has been used in drug-refractory AF (7,8). These two novel pacing methods can reduce global atrial activation time, eliminate conduction delays encountered by premature atrial beats that initiate AF and prevent AF initiation with programmed atrial stimulation (9,10). With long-term application in combination with antiarrhythmic drugs, dual-site RA pacing has been shown to increase arrhythmia-free intervals and reduce progression to permanent AF. The optimal pacing method alone or in combination with antiarrhythmic drug therapy with respect to AF prevention, patient safety and pacing mode tolerance in a symptomatic AF population is unknown. In 1996, we initiated an intermediate-term, prospective randomized crossover single blind trial to study the safety, tolerance and effectiveness of overdrive high RA and dual-site RA pacing as compared with support pacing in patients with symptomatic AF and bradyarrhythmias in whom permanent cardiac pacing was indicated.

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METHODS

Structure of the trial. The Dual-Site Atrial Pacing to Prevent Atrial Fibrillation (DAPPAF) trial enrolled patients from 13 clinical sites in North America (Appendix). The protocol was approved by institutional review committees, the U.S. Food and Drug Administration and monitored by an independent data safety and monitoring board.

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Abbreviations and Acronyms

AF = atrial fibrillation
DAPPAF = Dual-Site Atrial Pacing for Prevention of Atrial Fibrillation
RA = right atrial

The trial was supported by a research grant from Medtronic, Inc. (Minneapolis, MN), and all investigators agreed to established conflict of interest standards (11). The trial design and techniques have been reported (12). The primary objectives of the study were to determine whether the dual-site RA pacing system and mode is safe, to compare the time-to-first recurrence of clinically significant symptomatic AF episodes and to compare the quality of life of patients among the three pacing modes. Patients who were 21 to 80 years of age with two or more symptomatic AF events in the previous three months with a spontaneous or drug-induced bradyarrhythmia requiring permanent pacing were included. Patients with implantable cardioverter-defibrillators, contraindications to pacemaker implantation or anticipated life expectancy <18 months were excluded. Enrolled patients underwent insertion of a dual-chamber rate-responsive pulse generator with programmable polarity to allow high RA only and dual-site RA pacing. The pacemaker is capable of automatic switching between dual chamber and ventricular pacing and has device memory for stored electrograms from AF events (8). Pulse generators were connected to two RA leads that were placed at the high RA and outside the coronary sinus ostium via a Y-connector, along with a right ventricular lead. Dual-site RA pacing was confirmed with typical inverted or biphasic P waves (8,9). Antiarrhythmic drugs were continued for AF suppression and stabilized for two weeks after device implantation. Patients were advised to maintain a stable drug regimen throughout the trial. Each patient was assigned to the three pacing modes, that is, dual-site RA overdrive, high RA overdrive or support pacing for six months each in a randomized sequence for a maximum total follow-up period of 18 months. Recommended lower rates for overdrive pacing were 80 beats/min for arrhythmia suppression. Modes selected for support pacing (randomized by center) were DDI at 50 beats/min to provide "low" rate atrial pacing or no atrial pacing using the VDI mode. These rates and modes were chosen to address clinical practice and previous clinical studies at the time of study initiation, which had not included a control arm to conclusively prove benefit of atrial pacing. They were designed to prevent symptomatic bradycardia yet minimize atrial pacing. Patients were crossed over to the next assigned mode by an investigator if they were intolerant to a mode (persistent low cardiac output symptoms, syncope or near syncope, congestive heart failure, symptomatic pacemaker syndrome) despite all efforts to maintain the mode or after two electrocardiographically documented symptomatic AF recurrences. Diaries were used to document symptoms. Quality-of-life measurements, two-dimensional echocardiographic and Doppler examinations were performed at study entry (baseline) and at every mode change. An AF symptom checklist, a health status questionnaire and the Ferrans and Powers Cardiac Version III quality-of-life index were used to assess quality-of-life (12).

Pacing systems and implantation. Pacemaker pulse generators and leads used in this study were approved and market released by the U.S. or Canadian governmental authorities. The technique for device insertion has been described (7,12). The protocol recommended a lower pacing rate of 80 beats/min for overdriven AF suppression. AF events were logged using programmed "high rate atrial events" defined as ≥10 beats at 180 beats/min with the time and date of the first seven episodes. Event counters up to 255 episodes and stored atrial electrograms were used to validate AF events. AF recurrences required patient symptoms and documentation of AF.

Study end points and analysis. The major study end points were safety, including adherence to pacing mode, the time-to-first symptomatic AF recurrence and quality-of-life measures for AF-related symptoms and general health. Secondary objectives included comparison of all AF episodes (symptomatic or asymptomatic) between these pacing modes and comparison of the two support pacing modes (DDI and VDI). The study design projected a doubling of time-to-first recurrence with high RA pacing and a further 50% increase with dual-site RA pacing for sample size calculations with a power level of 80%. The Data Safety Monitoring Board and an events subcommittee adjudicated events and monitored patient safety. An intention to treat analysis was used with Kaplan-Meier actuarial survival curves being used to present outcome in each pacing mode. Statistical significance of unpaired and paired data was performed to allow for censoring as a result of crossover in each pacing mode. A relative risk assessment using hazard ratios from an extended Cox model was used for significance for unpaired data. Patients undergoing early crossover in a given mode were eliminated from paired analysis. A generalized Wilcoxon sign test was used for paired data comparisons between modes. Multiple comparisons for the SF-36 data had their critical p values adjusted for this analysis.

Prospectively determined subgroup analyses included antiarrhythmic drug use, and additional subgroup analyses were performed on individual baseline variables, including bradycardia indication, concomitant cardiovascular disease, AF event history and by center. Clinically relevant composite end points for efficacy and safety of individual pacing modes were not predetermined and were selected by the investigators at study completion before final data analysis. Subgroup analysis for asymptomatic AF episodes was only performed in patients with >14 days follow-up in each arm, with either <255 mode switch or high rate events during both arms or if ≥255 events in one arm had a comparable period of observation in the other arm.

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RESULTS

Of the 120 patients enrolled, two patients declined device insertion. Seventy-three men and 45 women with a mean age of 66 ± 11 years were randomized. They had recurrent, symptomatic AF, with paroxysmal AF episodes in 82 patients, persistent AF episodes for >72 h in 30 patients and with persistent AF of >30 days in duration in 6 patients. Ninety-two patients had cardiovascular disease, with coronary disease in 36, systemic hypertension in 69, valvular disease in 21 and cardiomyopathy in 14. Their mean left atrial diameter was 40 ± 6 mm, RA diameter 42 ± 9 mm and the left ventricular ejection fraction was 50 ± 12%. Pacing indications were sinus bradycardia (n = 64), sinus arrest (n = 18), drug-induced bradycardia (n = 23), asymptomatic sinus node dysfunction (n = 9), carotid sinus hypersensitivity (n = 1) or other conditions (n = 11). Symptomatic AF event frequency at enrollment was ≥1 event per day in 40 patients, weekly in 44 patients and monthly or less in 34 patients. Antiarrhythmic therapy included class 1 drugs in 24 patients, class 3 drugs in 48 patients, beta-blockers in 33 patients, calcium blockers in 15 patients and digoxin in 29 patients.

Pacemaker system insertion and antiarrhythmic drug selection. The pacing threshold for dual-site RA pacing was higher than high RA pacing (1.3 ± 0.9 vs. 0.9 ± 0.7 V at 0.5 ms pulse duration, $p < 0.05$). This was due to the higher impedance in dual-site RA pacing (833 ± 297 vs. 578 ± 229 ohms, $p < 0.05$). The mean pacing lower rate in the support arm was 55 ± 13 beats/min with 23 ± 29% ventricular pacing. In the high RA pacing arm, the mean lower rate was 79 ± 5 beats/min, similar to the dual-site RA pacing arm at 79 ± 4 beats/min ($p > 0.2$). The upper rate during high RA and dual-site RA pacing was also comparable (132 ± 8 vs. 131 ± 7 beats/min, $p > 0.2$). The percent atrial pacing achieved, determined by both programming and AF suppression, was lower in high RA (71 ± 31%) than in dual-site RA pacing (78 ± 27%, $p < 0.02$), whereas ventricular pacing was comparable (94 ± 10% vs. 91 ± 18% respectively, $p > 0.05$).

Tolerance and complications of individual pacing modes. Patient tolerance of an individual pacing mode assessed by time-to-crossover was greater with dual-site RA as compared with high RA pacing ($p = 0.006$) or support pacing ($p < 0.001$) (Fig. 1A, Table 1). This was also greater in high RA than support pacing ($p < 0.001$). Thus, follow-up was longer in the dual-site RA pacing mode as compared with high RA pacing mode (5.8 ± 2.9 vs. 4.7 ± 2.3 months, $p < 0.01$). Both overdrive modes achieved a longer follow-up as compared with the support pacing (3.3 ± 2.8 months, $p < 0.001$). After randomization, patients failed to tolerate or complete the selected mode most often in support pacing (56 patients) as compared with high RA pacing (31 patients, $p < 0.05$ vs. support) or dual-site RA pacing (21 patients, $p < 0.05$ vs. support, $p < 0.05$ vs. high RA pacing). Crossover was due to intolerance of the bradycardia associated with low demand pacing rate, recurrent symptomatic AF, loss of atrioventricular synchrony with pacemaker syndrome or adverse events (Table 1). Mode-related adverse events occurred in 21 patients in support, 11 patients in the high RA pacing and 15 patients in dual-site RA pacing ($p > 0.2$) (Table 1). Overall adverse event-free survival was greater in dual-site RA pacing as compared with support pacing ($p = 0.007$) but not to high RA pacing ($p = 0.75$) or when high RA pacing was compared with support pacing ($p = 0.15$). There were four deaths during the study and no stroke events. Lead dislodgements at the coronary sinus and high RA locations were infrequent (incidence 1.7%), and their incidence was comparable between locations ($p > 0.2$)

Eight-eight percent of patients were discharged on antiarrhythmic drugs, which were maintained as a stable regimen throughout the three pacing modes in 76.4% of the patients. Changes in antiarrhythmic medications occurred in 29 patients during the study, and these were comparably distributed among the modes ($p > 0.1$).

Prevention of recurrent AF. Mean total study follow-up was 12.1 ± 6.9 months with unequal periods in the treatment arms as a result of crossovers, study end points or adverse events. This resulted in a decreased AF recurrence rate (38.5% in the support mode and 33.7% in the high RA pacing mode) and significant reduction in paired data samples for analysis as indicated the figures. Relative risk (hazard ratio) analyses using the Cox model permitted inclusion of overall study data. Despite reduced event rates, in the entire study population the time-to-first symptomatic recurrence of AF trended to be longer in the dual-site RA pacing mode than the support mode (Cox proportional hazards survival ratio 0.715, paired Wilcoxon $p = 0.07$, Fig. 1B). This was significantly longer in the subgroup treated with class 1 or 3 antiarrhythmic drugs (Cox proportional hazards survival ratio 0.646, paired Wilcoxon $p = 0.011$) (Fig. 2). In contrast, high RA pacing showed no benefit compared with support pacing, irrespective of the presence or absence of antiarrhythmic drugs (Fig. 2).

Comparison of dual-site RA and high RA pacing for freedom from all symptomatic AF events in the entire study population did not show significant benefit by paired analysis but did demonstrate a modest relative risk reduction of 16.5%, although this did not achieve significance (Cox proportional hazards survival ratio 0.835, paired Wilcoxon $p = 0.175$). In drug-treated patients receiving class 1 or 3 antiarrhythmic drugs who comprised 82% of the study population, dual-site RA pacing did prolong time-to-first AF recurrence, with a risk reduction of 33% now approaching significance as compared with high RA pacing (Cox proportional hazards survival ratio 0.669, paired Wilcoxon $p = 0.06$). There was no improvement in the absence of drug therapy (Fig. 2). In patients who developed recurrent AF, the median time-to-recurrence was longest in dual-site RA pacing (1.77 months) compared with high RA pacing

Table 1. Adverse Events in Randomized Atms

Adverse Event Category	Support	High RA	Dual Site	Total
Related to pacing mode				
Pacemaker syndrome (symptoms, e.g., dizziness, dyspnea, angina, and other)	15	9	11	35
Syncope	5	1	1	7
Rate control with AV node ablation	1	1	1	3
Far field R wave over sensing	0	0	2	2
Total mode-related adverse events	21	11	15	47
Unrelated to pacing mode				
Implant related				
Cellulitis, pocket hematoma/seroma				6
Infection				1
Other implant related				2
Lead dislodgements				5
Non-implant related				
Unrelated surgery				3
Other				1
Randomized arm when initially detected	2	9	7	18
Total adverse events	23	20	22	65

(0.62 months, $p < 0.09$) or support pacing (0.44 months, $p < 0.05$ vs. dual RA, $p > 0.7$ vs. high RA).

In patients on class 1 or 3 antiarrhythmic drugs with a baseline symptomatic AF event rate ≤1 per week (78 patients, 66% of the study population), there was a significantly longer AF-free survival with dual-site RA pacing as compared with high RA pacing (Cox proportional hazards survival ratio 0.46, paired Wilcoxon $p = 0.006$,) or support pacing (Cox proportional hazards survival ratio 0.623, paired Wilcoxon $p = 0.004$) (Fig. 3). There was no benefit of high RA pacing as compared with support pacing in this subgroup. In patients reporting daily AF, dual-site RA pacing displayed no benefit compared with support or high RA pacing. Using data only from the first randomized treatment arm showed similar trends, but statistical power was lower.

Quality-of-life and AF symptoms. AF symptom scores were significantly lower in the high RA pacing mode ($p < 0.001$) and trended to be lower in dual-site RA ($p = 0.09$) compared with the support mode, but no differences existed between dual-site RA and high RA pacing (Fig. 4). Quality-of-life measurements for physical health measures showed improvement in high RA pacing compared with baseline (40 ± 11 vs. 35 ± 10, $p < 0.05$) whereas mental health measures showed improvement in all three arms compared with baseline (support = 48 ± 11, high RA 51 ± 9, dual-site RA 50 ± 10 vs. 38 ± 11, $p < 0.05$).

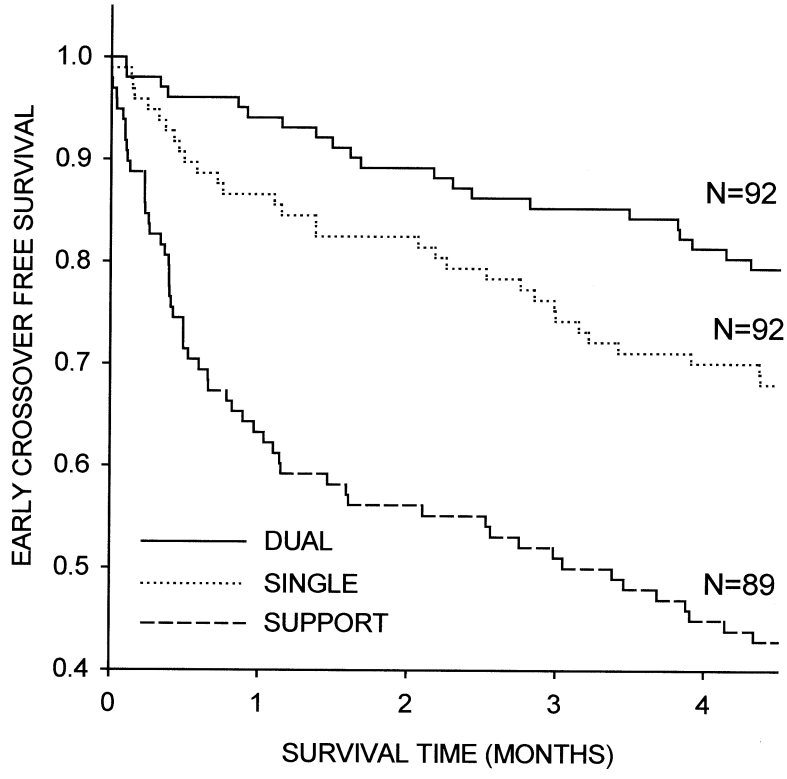
Overall efficacy and tolerance of pacing modes. The major composite end point used time-to-first AF recurrence coupled with maintenance in a randomized pacing mode. Dual-site RA pacing was superior to high RA pacing (Cox proportional hazards survival ratio 0. 687, paired Wilcoxon $p < 0.05$) and to support pacing (Cox proportional hazards survival ratio 0.582, paired Wilcoxon $p < 0.001$). High RA pacing was also superior to support pacing (Cox proportional hazards survival ratio 0.504, paired Wilcoxon $p < 0.001$). Both dual-site RA pacing and high RA pacing were superior to support pacing for time-to-first AF recurrence coupled with time-to-adverse event ($p < 0.05$).

Effect of overdrive pacing mode on symptomatic and asymptomatic AF frequency. Patients meeting the subgroup analysis criteria showed a significant decrease in mode switch events and detected high-rate atrial events with dual-site RA pacing compared with high RA pacing. Mode switch events could be assessed in 23 patients and decreased from a mean value of 234 ± 262 events (mean 2.6 ± 4.9 events/day, median 1.401 events/day) in high RA pacing to 86 ± 74 events (mean 0.71 ± 0.88 events/day, median 0.351 events/day) in dual-site RA pacing ($p < 0.01$, signed rank Wilcoxon $p = 0.0017$). High-rate atrial events met inclusion criteria in 16 patients and decreased from a mean value of 194 ± 147 events (mean 3.0 ± 3.5 events/day, median 1.915 events/day) in high RA pacing to 70 ± 92 events (mean 0.6 ± 1.0 events/day, median 0.181 events/day) in dual-site RA pacing ($p < 0.01$, signed rank Wilcoxon $p = 0.0042$) (Fig. 5).

DISCUSSION

This study was designed as an intermediate term comparison of three different pacing modes in patients with recurrent, paroxysmal or persistent AF. The support arm was the control arm with minimal atrial pacing in a highly symptomatic population. The main findings of the study include:

1. Insertion of an additional atrial lead in dual-site RA pacing systems has acceptable safety and stability compared with standard DDDR pacing systems.
2. Improved adherence to pacing mode with dual-site RA pacing compared with both high RA and support pacing in an AF population.



A

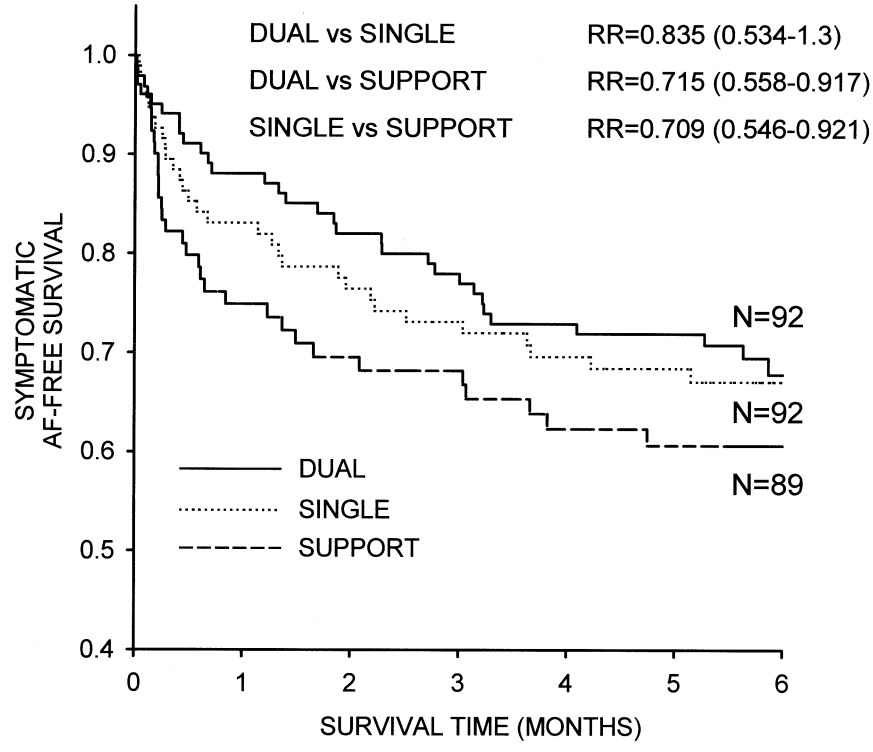
	Paired Wilcoxon sign test
Dual vs Single, (n=35)	p=0.006
Dual vs Support, (n=55)	p<0.001
Single vs Support, (n=54)	p<0.001

Figure 1. (A) Freedom from crossover within 4.5 months of entering randomized treatment phase for each pacing mode. The percentage of patients surviving in the mode is tabulated on the Y-axis and the follow-up duration in the mode on the X-axis. Dual right atrial (RA) pacing shows a higher proportion of patients able to remain in the randomized treatment mode as compared with other modes. Dual, dual-site RA pacing; single, high RA pacing; support, demand pacing in atrium or ventricle at low support rate. **(B)** Freedom from all symptomatic atrial fibrillation (AF) in each randomized pacing mode in the entire study population. Dual RA pacing but not high RA pacing shows a trend to prolongation of time interval to AF recurrence.

3. Improved outcome with dual-site atrial pacing both for adherence to the pacing mode and efficacy in the presence of class 1 or 3 antiarrhythmic drug therapy, especially in patients with <1 symptomatic AF event per week.
4. Reduction in both symptomatic and asymptomatic AF events in the patient subgroup whose device datalogs could be compared in the high RA and dual-site RA pacing modes.
5. Absence of efficacy with high RA pacing compared with the support mode possibly related to study power but improved adherence to the mode.
6. Poor adherence and adverse effect profile with support pacing in this relatively brief follow-up period.
7. Comparative analysis of AF prevention between pacing modes is impacted greatly by poor adherence and high crossover rates in support and overdrive high RA pacing in this highly symptomatic population.

Safety of dual-site RA pacing and coronary sinus ostium lead placement. Adverse event rates were comparable for high and dual RA pacing. Lead dislodgement at for coronary sinus and high RA sites had comparable frequency with a low incidence sufficient to justify the conclusion that placement of an additional screw in active fixation lead at the coronary sinus ostium is safe, has comparable stability to high RA locations and has an incremental risk of an additional atrial lead insertion and current drain (Table 1). Poor tolerance of support pacing was related to either intolerance of pacing rate, recurrent AF or pacemaker syndrome. Despite theoretical concerns, ischemia or proarrhythmia were not observed with overdrive pacing, which was well tolerated. Stroke and mortality were within reported values.

Implementation of long-term atrial pacing. This study shows the challenge in maintaining patients with AF and bradyarrhythmias in support and standard high RA pacing



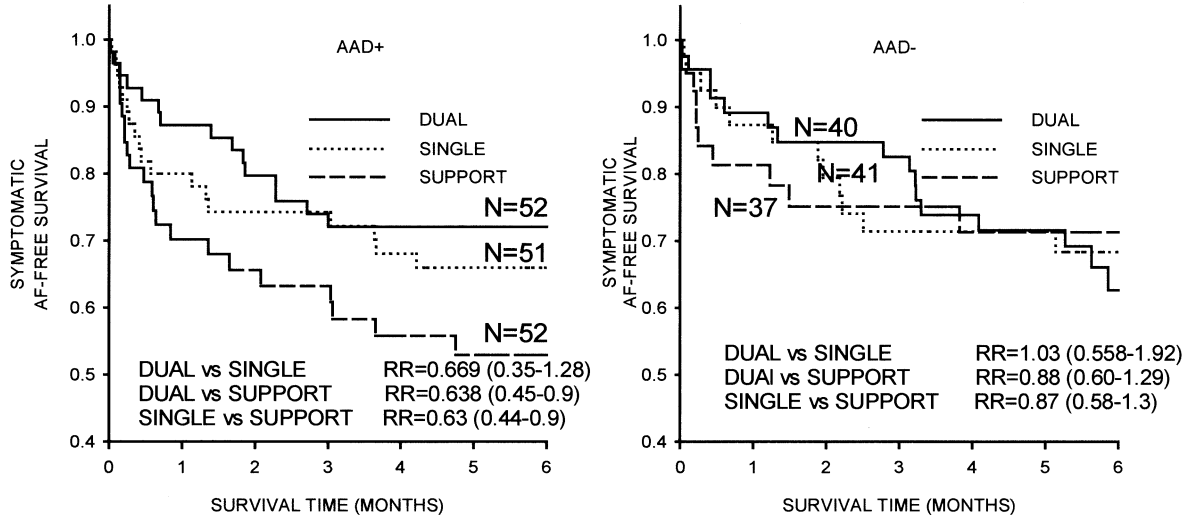
B

	Paired Wilcoxon sign test
Dual vs Single, (n=35)	p=0.175
Dual vs Support, (n=38)	p=0.073
Single vs Support, (n=37)	p=0.188

Figure 1. Continued.

in the DDDR mode. In a population of sick sinus syndrome patients in the Mode Optimization Study, Lamas et al. (13) demonstrated a high crossover rate exceeding 30% at one year with ventricular demand pacing. Over 50% of patients in support pacing and 30% in high RA pacing could not maintain the pacing mode beyond four months in our AF population. Thus, assessment of efficacy of preventive pacing for any significant period is unlikely to be achieved. This experience also suggests that substantial preventive pacing cannot be achieved on a long-term basis in these modes. These data may also require significant adjustment of sample size and/or duration for paired data analysis with acceptable power in atrial pacing trials in symptomatic AF populations. Adherence to dual-site RA pacing, a measure of adverse events and symptomatic AF recurrences leading to crossover, was clearly superior to both support and high RA pacing. Thus, long-term application of this atrial pacing mode is feasible and should favor its application in this population.

Efficacy of high RA and support pacing for AF prevention. Previous studies of high RA pacing have noted that relatively long follow-up periods show lower incidence of AF as compared with ventricular pacing in patients with bradycardias without antecedent AF (9,10). However, proarrhythmia with ventricular pacing cannot be excluded. We minimized the potential proarrhythmic effect of ventricular pacing by maintaining a low percent pacing in the support arm. We also improved the detection of AF recurrences with electrogram confirmation to validate patient symptoms. Unlike other recent trials in whom AF recurrences of <10 min in duration were not included, our analysis includes any symptomatic recurrence (14). In contrast to populations with bradycardia, our study suggests high RA pacing is preferable to support pacing in an AF population because of better patient tolerance rather than efficacy. These data suggest that in the population with recurrent symptomatic AF and bradycardias, the benefits of high RA pacing cannot be demonstrated in the study period in question. It is unclear whether a larger sample size or a longer observation period would show greater efficacy because a weak trend to benefit was seen in the presence of antiarrhythmic drugs. However, support pacing is the least preferred mode in this patient population. This may be due to high AF recurrence rates and potentially deleterious



	Paired Wilcoxon sign test			Paired Wilcoxon sign test
Dual vs Single, (n=19)	p=0.064		Dual vs Single, (n=16)	p=1.000
Dual vs Support, (n=23)	p=0.011		Dual vs Support, (n=15)	p=1.000
Single vs Support, (n=25)	p=0.108		Single vs Support, (n=12)	p=1.000

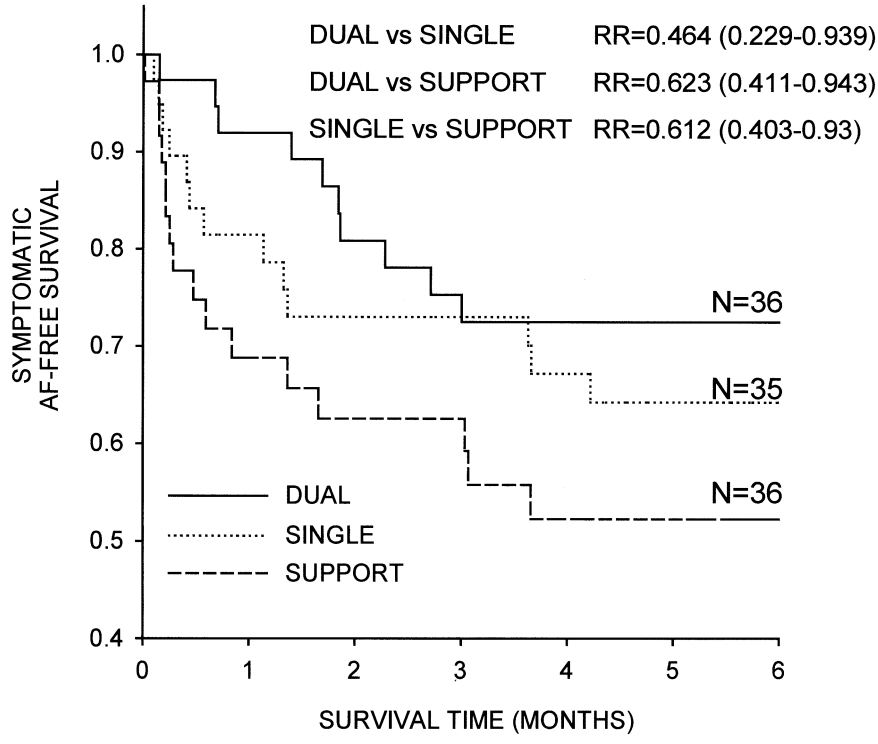
Figure 2. Freedom from all symptomatic atrial fibrillation (AF) in each randomized pacing mode in study population receiving concomitant class 1 or 3 antiarrhythmic drugs (AAD+ on the **left**) or without concomitant drug therapy (AAD− on the **right**). Dual right atrial (RA) pacing but not high RA pacing shows prolongation of time interval to AF recurrence as compared with support pacing and a trend to prolongation as compared with high RA pacing in drug-treated patients. There is no difference in outcome in patients on any randomized pacing mode without concomitant drug therapy. AAD = antiarrhythmic drug.

hemodynamic effects of right ventricular apical pacing modes.

Dual-site RA pacing improved efficacy and tolerance. Dual-site RA pacing showed incremental benefits with respect to AF prevention derived almost exclusively in the large (82%) subgroup receiving antiarrhythmic drug therapy. Furthermore improved patient tolerance led to the least attrition in patient compliance with the pacing mode. This supports the use of this pacing mode for long-term efforts at drug-refractory AF prevention with pacing techniques.

Dual-site RA pacing reduced the incidence of recurrent symptomatic AF in specific AF population subgroups as well as prolonged time-to-recurrence in patients who experienced recurrent AF during the study period in comparison to the other modes, specifically including high RA pacing. Reduced AF recurrence rates were observed in class 1 or 3 drug-treated individuals and were particularly significant in patients with frequent but not daily AF (7,15). These comprised the majority of the sample in this study. Benefits with respect to symptomatic and asymptomatic AF were also documented by device datalogs in this mode compared with high RA pacing. These data are best judged for their significance in the light of the reduced AF event incidence in the comparison arms resulting from the reduced follow-up period as a result of high crossover rates in these arms. These efficacy benefits coupled with the observation that the dual-site RA pacing mode may have the highest likelihood of long-term compliance make it preferable to the other pacing modes.

Clinical relevance of the dual-site RA pacing technique. The clinical relevance of this incremental efficacy in AF prevention with dual-site RA pacing can be best judged in comparison to similar trials with antiarrhythmic drugs and lack of benefit with respect to AF prevention in the high RA pacing arm. The drug-treated dual-site RA pacing group had freedom from AF recurrence was 80%, 72% and 72% at two, four and six months of follow-up, often in drug-refractory patients. In previous reports during flecainide, propafenone or sotalol therapy, freedom from symptomatic AF at six months was 30% to 60%, 45% to 60% and 40% respectively (6,7,14,16). For amiodarone, this value is estimated at 75% after censoring early recurrences (14). Thus, dual-site RA pacing provides clinically relevant level of incremental efficacy for AF suppression in this population.



	Paired Wilcoxon sign test
Dual vs Single, n=12	p=0.006
Dual vs Support, n=16	p=0.004
Single vs Support, n=16	p=0.238

Figure 3. Freedom from all symptomatic atrial fibrillation (AF) in each randomized pacing mode in study population receiving concomitant class 1 or 3 antiarrhythmic drugs with frequent (weekly events to two events in three months) AF at baseline. Dual right atrial (RA) pacing shows prolongation of time interval to AF recurrence as compared with high RA or support pacing in these patients.

In comparison with standard high RA pacing, benefits of dual-site RA pacing with respect to AF prevention become apparent, even in the relatively short observation period of this study, in patients reporting frequent (weekly or less events) but not daily AF. This is a large drug-refractory patient population, which comprised a majority of our study patients. In these patients, the addition of this pacing system improved outcome significantly even in the short-term, with the potential for long-term benefit. In contrast, this study and other studies have not demonstrated any benefit of high RA pacing for prevention of symptomatic AF (4).

AF recurrences during dual RA pacing diminish with longer-term follow-up (15). Early recurrence(s) of AF during dual RA pacing do not predict long-term symptomatic AF suppression (15). Thus, a long-term therapeutic strategy with dual RA pacing could require termination of early AF recurrences, allowing for pacing to progressively diminish AF recurrence rates and restore rhythm control in drug-treated patients (15). For best results, the dual-site RA pacing technique should be applied in patients with brady-arrhythmias and symptomatic and refractory AF, in whom antiarrhythmic drug therapy can and is being continued. Patients with paroxysmal and persistent AF were included in this study.

Mechanism of efficacy. Efficacy of dual-site RA pacing may be due to a variety of synergistic antiarrhythmic effects (15,17). Continuous overdrive atrial pacing can suppress atrial premature beats, triggering AF and causing atrial remodeling (17). Lower rates of 80 beats/min can also eliminate pauses preceding AF onset. Dual-site RA pacing abbreviates intra-atrial conduction for the paced as well as for premature atrial beats, preventing AF initiation (9,10,18). Drugs may increase AF organization with increased vulnerability to electrical termination (19). Resynchronization of atrial regions by dual-site RA pacing diminishes heterogeneity of refractoriness and in postoperative AF has reduced recurrence rates (20). Analysis of echocardiographic data from this study, which is being reported separately, shows a decrease in left ventricular ejection

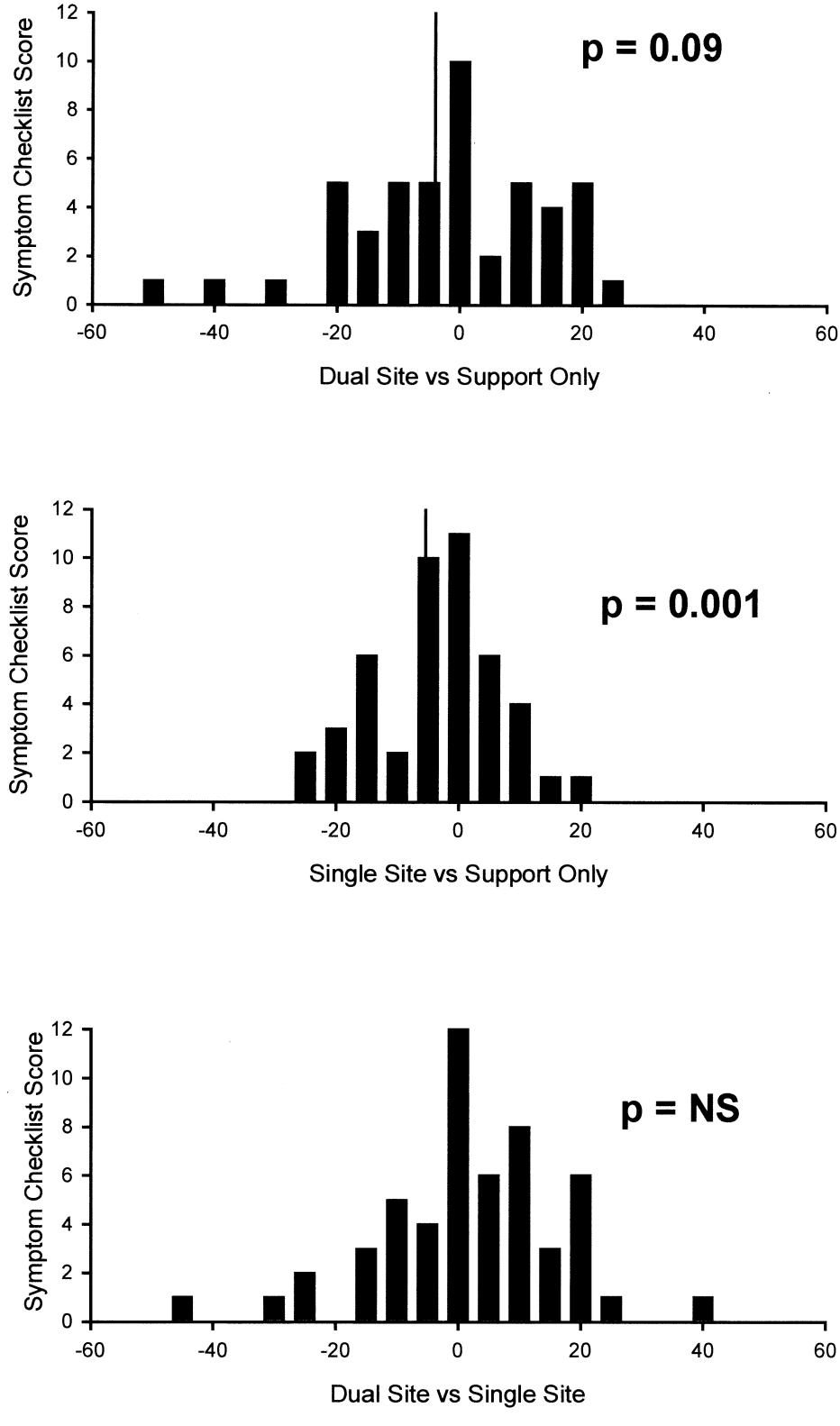


Figure 4. Quality-of-life in the study population at baseline and in each randomized treatment mode for individual measures. Atrial fibrillation symptom checklist (paired analysis) in each randomized mode shows the benefits of both overdrive pacing modes as compared with support pacing.

fraction and left atrial enlargement with high RA pacing in the DDDR mode, which is completely attenuated by dual-site RA pacing (21). Dual-site RA pacing also improved left atrial transport.

Potential role of AF event frequency. Our study population is reflective of a large segment of the general AF pool, but it differed from previous studies in enrolling symptomatic AF patients (4,5). Our median AF-free interval was

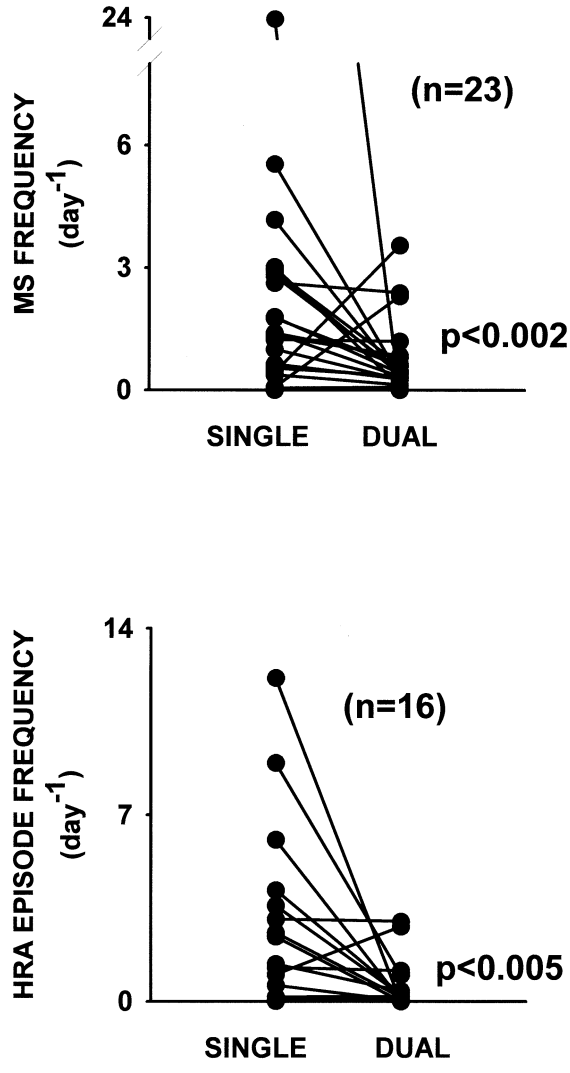


Figure 5. Comparison of symptomatic or asymptomatic atrial fibrillation (AF) events meeting high rate atrial (HRA) event detection criteria in the dual-site right atrial (RA) pacing or high RA pacing arms of the study. Data are presented as mean values per day. A significant reduction in mean event frequency is observed for both AF end points in dual-site RA pacing arm as compared with the high RA pacing arm, suggesting benefit with respect to both symptomatic and symptomatic AF. MS = made switch.

weekly at study entry. These patients are routinely treated with antiarrhythmic drugs and show incremental benefit with the addition of dual RA pacing to drug therapy. However, the role of pacing in patients with daily AF may be more limited as a result of the high density of triggers, a very vulnerable substrate and limited opportunity to establish continuous pacing. Incessant triggers in this group may not be fully suppressed by pacing and require additional interventions. Substrate remodeling because of rapid atrial rates in AF may make it very vulnerable to AF even with a few residual triggers. Our end point may also be insensitive to reductions in AF frequency, burden or progression to permanent AF in this group. Alternative approaches, such as ablation, may be used to reduce AF event rate before pacing.

This study supports the concept of incremental therapy of the AF patient with hybrid drug and pacemaker therapy in our study population. A paradigm shift in the treatment of drug refractory AF in patients with bradycardias using combined pharmacologic and dual-site RA pacing will require demonstration of long-term efficacy in AF prevention and applicability of this technique.

Study limitations. This study, as in previous studies in patients with highly symptomatic tachyarrhythmias, did not randomize antiarrhythmic drug usage or sequences. Although participants were blinded to the randomized mode, it is difficult to blind investigators in pacing trials because electrocardiographic recordings identify the pacing mode. Crossovers in the support arm reduced event rates and power, suggesting end points based on multiple symptomatic AF recurrences are unlikely to obtain compliance. Thus, other clinically relevant end points such as our composite end points, hospitalization and cardioversion may be important in AF populations. Finally, three paired unadjusted comparisons were performed between treatment arms for time-to-symptomatic AF recurrence, and the type 1 error associated with this hypothesis could be inflated.

Conclusions. We conclude that in patients with bradycardias and AF on antiarrhythmic drugs, dual-site RA pacing prolonged and high RA pacing trended to prolong time-to-recurrent AF compared with support pacing. In patients with weekly or less frequent symptomatic AF recurrences on antiarrhythmic drug therapy, overdrive dual-site RA pacing provides more effective prevention of recurrent AF and improves tolerance for pacemaker therapy with comparable safety. Larger studies of the two overdrive pacing methods in combination with drugs and with cost comparisons are needed. This trial supports longer-term evaluation of overdrive dual-site RA pacing in other drug-treated AF populations. It does not support the use of atrial pacing as monotherapy in this symptomatic AF population.

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REFERENCES

1. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: The Framingham Heart Study. Circulation 1998;98:946–52.
2. Anderson JL, Gilbert EM, Alpert BL, et al. Prevention of symptomatic recurrences in patients with paroxysmal atrial fibrillation in patients initially tolerating antiarrhythmic therapy: a multicenter double blind crossover study of flecainide and placebo with transtelephonic monitoring. Circulation 1989;80:1557–70.
3. Antman EM, Beamer AD, Cantillon C, McGowan N, Goldman L, Friedman P. Long-term oral propafenone therapy for suppression of refractory symptomatic atrial fibrillation and atrial flutter. J Am Coll Cardiol 1988;12:1005–11.
4. Gillis AM, Connolly SJ, Lacombe P, et al. Randomized crossover comparison of DDDR versus VDD pacing after atrioventricular junction ablation for prevention of atrial fibrillation. The atrial pacing peri-ablation for paroxysmal atrial fibrillation (PA (3)) study investigators. Circulation 2000;102:736–41.

5. Andersen HR, Nielsen JC, Thomsen PEB, et al. Long-term follow-up of patients from a randomized trial of atrial versus ventricular pacing for sick-sinus syndrome. Lancet 1997;305:1210–16.
6. Connolly SJ, Kerr CR, Gent M, et al. Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. Canadian Trial of Physiologic Pacing Investigators. N Engl J Med 2000;342:1385–91.
7. Saksena S, Prakash A, Hill M, et al. Prevention of recurrent atrial fibrillation with chronic dual-site right atrial pacing. J Am Coll Cardiol 1996;28:687–94.
8. Daubert C, Mabo PH, Berder V, Gras D, Leclercq C. Atrial tachyarrhythmias associated with high degree interatrial conduction block: prevention by permanent atrial resynchronization. Eur J Card Pacing Electrophysiol 1994;1:35–44.
9. Prakash A, Delfaut P, Krol RB, Saksena S. Regional right and left atrial activation patterns during single and dual-site atrial pacing in patients with atrial fibrillation. Am J Cardiol 1998;82:1197–204.
10. Prakash A, Saksena S, Hill M, et al. Acute effects of dual-site right atrial pacing in patients with spontaneous and inducible atrial flutter and fibrillation. J Am Coll Cardiol 1997;29:1007–14.
11. Healy B, Campeau L Gray R, et al. Conflict of interest guidelines for a multicenter clinical trial of treatment after coronary artery bypass graft surgery. N Engl J Med 1989;320:949–51.
12. Fitts SM, Hill MRS, Mehra R, et al., for the DAPPAF Phase 1 Investigators. Design and implementation of the Dual Site Atrial Pacing to Prevent Atrial Fibrillation (DAPPAF) clinical trial. J Intervent Card Electrophysiol 1998;2:139–44.
13. Lamas GK, Lee KL, Sweeney MO, et al. Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. N Engl J Med 2002;346:1854–62.
14. Roy D, Talajic M, Dorian P, et al. Amiodarone to prevent atrial fibrillation. N Engl J Med 2000;342:813–920.
15. Delfaut P, Saksena S, Prakash A, Krol RB. Long-term outcome of patients with drug-refractory atrial flutter and fibrillation after single and dual-site right atrial pacing for arrhythmia prevention. J Am Coll Cardiol 1998;32:1900–8.
16. Van Gelder I, Crijns HJGM, Van Gilst WH, Van Wijk LM, Hamer HPM, Lie KI. Efficacy and safety of flecainide acetate in the maintenance of sinus rhythm after electrical cardioversion of chronic atrial fibrillation or atrial flutter. Am J Cardiol 1989;64:1317–21.
17. Murgatroyd FD, Nitzsche R, Slade AKB, et al. A new pacing algorithm for overdrive suppression of atrial fibrillation. PACE 1994; 17:1966–73.
18. Yu WC, Chen SA, Tai CT, Feng AN, Chang MS. Effects of different atrial pacing modes on atrial electrophysiology: implicating the mechanism of biatrial pacing in prevention of atrial fibrillation. Circulation 1997;96:2992–6.
19. Wijffels MC, Dorland R, Mast F, Allessie MA. Widening of the excitable gap during pharmacological cardioversion of atrial fibrillation in the goat: effects of cibenzoline, hydroquinidine, flecainide, and d-sotalol. Circulation 2000;102:260–7.
20. Fan K, Lee KL, Chiu CSW, et al. Effects of biatrial pacing in prevention of postoperative atrial fibrillation after coronary bypass surgery. Circulation 2000;102:755–60.
21. Prakash A, Saksena S, Ziegler P, et al., for the DAPPAF investigators. Dual-site atrial pacing for prevention of atrial fibrillation (DAPPAF) trial: echocardiographic evaluation of atrial and ventricular function during a randomized trial of support, high right atrial and dual site right atrial pacing (abstr). PACE 2001;24:553.

APPENDIX

For a complete list of Investigators and Participating Institutions, please see the September 18 issue of *JACC* at www.cardiosource.com/jacc.html.